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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/024,450	12/17/2001	Shi Huang	P-LJ 5101	6235

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EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	10

DATE MAILED: 03/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/024,450	HUANG ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *1-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed April 11, 2003. Currently, claims 1-23 are pending. Claims 1-16 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Applicant's election with traverse of Group II in Paper No. 9 is acknowledged. The response traverses the rejection because "a thorough search of the claims of Group II likely will result in art relevant to the examination of the claims of Group I." This argument has been thoroughly reviewed, but is not found persuasive because the search of Group II is not coextensive of Group I. A prima facie case of burden has been established by the examiner upon indication of separate classifications.

The requirement is still deemed proper and is therefore made FINAL.

This application contains claims 1-16 drawn to an invention nonelected with traverse in Paper No. 9. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

3. This application claims priority to provisional application 60/256,582, filed December 19, 2000.

Drawings

4. The drawings are objected to because figure 1 comprises more than one part which is not identified in the brief description of drawings. For example, the brief description of drawings on page 5 of the instant specification does not set forth 1A, 1B etc.

Specification

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

On page 20-21 for example, the specification contains hyperlinks.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 17-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining MSI status of a colorectal tumor, a gastric tumor and an endometrial tumor, comprising determining in the tumor the number of adenosine (A) nucleotides in a poly(A) tract located at positions 4393-4400 of SEQ ID NO: 3 or 4582-4590 of SEQ ID NO: 3, where a decrease of one or two adenosine nucleotides in said poly(A) tract indicates that the tumor is MSI-positive, does not reasonably provide enablement for a method of determining MSI status of any tumor by determining the number of adenosine nucleotides in any poly(A) tract of a RIZ nucleic acid where any abnormality is indicative of MSI-positive tumors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of determining MSI status of a tumor, comprising determining in said tumor the number of adenosine (A) nucleotides in a poly(A) tract of a RIZ nucleic acid molecule wherein an abnormal number of adenosine

nucleotides in said RIZ poly(A) tract indicates the tumor is MSI-positive. The invention is is an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass a method of determining the MSI status of any tumor using any poly(A) tract in RIZ using any abnormality in the number of adenosine nucleotides of the tract.

The unpredictability of the art and the state of the prior art

The art teaches that reliable studies suggest there is a great difference in the observed frequency from one marker (i.e. one dinucleotide compared to a similar dinucleotide) to another and from one type of cancer to another (e.g., bladder cancer versus lung cancer). Boland et al. (Cancer Research, Vol. 58, pages 5248-5257, November 1998) teaches there are two types of noncolonic non-HNPCC tumors that display elevated frequencies of MSI. The first group is found in gastric, endometrial which has a similar phenotype to MSI in colorectal cnacer and displays instability at mononucleotide markers and to a lesser degree at larger repeats (page 5253, col. 2). The second group of noncolonic non-HNPCC tumors display elevated frequencies in non-HNPCC tumors of different types such as lung, bladder and head/neck. Each of the cancers described in the instant specification are within the first group.

The art teaches detection of a A8 and an A9 poly(A) tract in RIZ as indicative of colorectal, gastric and endometrial tumors. Chadwick teaches sequence analysis revealed frequent frameshift mutations of the RIZ gene. The mutations consisted of 1-

or 2-bp deletions of a coding (A)8 or (A)9 tract and were confined to microsatellite-unstable colorectal tumors, being present in 9 of 24 (37.5%) primary tumors (abstract). The coding sequence of RIZ showed hypermutable tracts of (A)8 and (A)9 in exon 8 of RIZ gene. In 9/24 (37.5%) of the MSI(+) HNPCC tumors, frameshifts were found in either the A8 or A9 tract. None of the 23 tested MSI(-) sporadic colorectal cancers contained mutation in either of the polyadenosine tracts indicating that these regions were mutational hotspots in MSI(+) tumors only (page 2665, col. 2). As seen in Figure 3, Chadwick teaches 1-bp or 2-bp deletions.

Moreover, Piao et al. (Cancer Research, Vol. 60, pages 4701-4704, September 2000) teaches studying RIZ mutations in sporadic cancers with microsatellite instability. Frameshift mutations in the two coding polyadenosine tracks of RIZ were found in 19/40 (48%) gastric carcinomas, 6/18 (33%) endometrial carcinomas, 14/51 (26%) of colorectal carcinomas and 7/13 (54% cell lines) (abstract)(limitations of Claims 22-23). Piao teaches using primers for the A8 and A9 tract to amplify the region and sequenced (page 4702-4703)(limitations of Claim 18-19). No mutations in the A8 or A9 track were found in 70 MSI (-) gastric carcinomas. Piao teaches that 1bp and 2bp deletions were observed (see Figure 1)(limitations of Claim 21).

Guidance in the Specification and Working Examples

The specification teaches that a scan of RIZ1 cDNA sequence revealed two potentially hypermutable polyadenosine tracts within its coding region in exon 8: one A8 tract at residues 4393-4400 of SEQ ID NO: , and one A9 tract at residues 4582-4590 of SEQ ID NO: 3.

The specification analyzes the poly(A)8 and 9 tracts and 9/24of MSI(+) HNPCC tumors contain a frameshift mutation. Non of the 23 tested MSI(-) sporadic colorectal cancers contained mutation in either polyadenosine tract (page 25).

The specification analyzes other known mononucleotide tracts in other genes and framesthis in these tracts were completely absent in the MSI(+) tumors.

Example II provides an analysis of frameshift mutations in poly(A) tracts in gastric cancers, endometrial cancers and colorectal cancers (page 30). RIZ mutations were detected in 19/40 (48%) of gastric cancers; 6/18 (33%) endometrial cancers; and 14/51 (26%) of colorectal cancers (page 31).

The specification discusses 1bp deletion and 2bp deletion (page 32). The specification fails to describe any additional abnormalities.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since determination of additional tumors, additional poly(A) tracts and additional normalities are encompassed by the instant claims. The specification teaches the presence of deletions of 1bp or 2bp within the polyadenosine tracts within its coding region in exon 8: one A8 tract at residues 4393-4400 of SEQ ID NO: , and one A9 tract at residues 4582-4590 of SEQ ID NO: 3. The specification does not provide for any abnormality. The specification fails to provide any guidance as to the determination of MSI status for an increase in adenosine number. The specification fails to provide any evidence that the poly(A)8 and 9 tracts gain adenosine and are indicative of MSI status. Further, the only abnormalities discussed are 1bp or 2bp deletions. Therefore while one could conduct additional experimentation to determine whether, e.g. increase in numbers of adenosine might be associated with, e.g. MSI status in all tumors, the outcome of such

research cannot be predicted, and such further research and experimentation are both unpredictable and undue.

Moreover, the prior art teaches that there are two general types of tumors that display elevated frequencies of MSI. The instant specification appears to teach gastric, colorectal and endometrial which are all common to the first group. The first group is also characterized by mononucleotide makers which is claimed. There is not indication that the poy(A) tracts would be predictive of those cancers which are typically classified in the second group, such as lung, bladder and head and neck cancer. Because the art clearly provides a categorization between a two groups of cancers and the markers which allows for determination of MSI status, it is unpredictable that any of the cancers within the second group of tumors would be associated in the same manner as the first group. The skilled artisan would be required to perform additional experimentation as to whether abnormalities of any variety including 1bp and 2bp deletions in the poly(A) tracts would be associated with lung, bladder, head and neck cancers, for example.

Finally, the claim is drawn to any poly(A) tract in a RIC nucleic acid molecule. The specification teaches scanning the RIZ1 cDNA sequence which revealed two potentially hypermutable polyadenosine tracts within its coding region in exon 8: one A8 tract at residues 4393-4400 of SEQ ID NO: , and one A9 tract at residues 4582-4590 of SEQ ID NO: 3. It is unpredictable whether the RIZ2 cDNA comprises any poly(A) tracts or whether the genomic DNA of RIZ comprises any poly(A) tracts. In the event that the skilled artisan identified an additional poly(A) tract, the skilled artisan would be required to perform additional experimentation to determine whether variations in the tract are related to MSI status. As noted above, while one could conduct such additional experimentation, the outcome of such research can not be predicted, and such further research and experimentation are both unpredictable and undue. This

would require inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability in the art is high, the specification provides one with no written description or guidance that leads one to a reliable method of determining MSI status. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains . Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of any working examples and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 17-19, 21-23 are rejected under 35 U.S.C. 102(a) as being anticipated by Chadwick (PNAS, Vol. 97, No. 6, pages 2662-2667, March 2000).

It is noted that the authorship of the Chadwick et al. reference is distinct from the inventorship of the instant application and that this rejection may be overcome by the filing of a 132 Katz-type declaration.

Chadwick teaches sequence analysis revealed frequent frameshift mutations of the RIZ gene. The mutations consisted of 1- or 2-bp deletions of a coding (A)8 or (A)9 tract and were confined to microsatellite-unstable colorectal tumors, being present in 9 of 24 (37.5%) primary tumors (abstract). The coding sequence of RIZ showed hypermutable tracts of (A)8 and (A)9 in exon 8 of RIZ gene. In 9/24 (37.5%) of the MSI(+) HNPCC tumors, frameshifts were found in either the A8 or A9 tract. None of the 23 tested MSI(-) sporadic colorectal cancers contained mutation in either of the polyadenosine tracts indicating that these regions were mutational hotspots in MSI(+) tumors only (page 2665, col. 2). As seen in Figure 3, Chadwick teaches 1-bp or 2-bp deletions.

8. Claims 17-19, 21-23 are rejected under 35 U.S.C. 102(a) as being anticipated by Piao et al. (Cancer Research, Vol. 60, pages 4701-4704, September 2000).

It is noted that the authorship of the Piao et al. reference is distinct from the inventorship of the instant application.

Piao et al. (herein referred to as Piao) teaches studying RIZ mutations in sporadic cancers with microsatellite instability. Frameshift mutations in the two coding

polyadenosine tracks of RIZ were found in 19/40 (48%) gastric carcinomas, 6/18 (33%) endometrial carcinomas, 14/51 (26%) of colorectal carcinomas and 7/13 (54% cell lines) (abstract)(limitations of Claims 22-23). Piao teaches using primers for the A8 and A9 tract to amplify the region and sequenced (page 4702-4703)(limitations of Claim 18-19). No mutations in the A8 or A9 track were found in 70 MSI (-) gastric carcinomas. Piao teaches that 1bp and 2bp deletions were observed (see Figure 1)(limitations of Claim 21).

Conclusion

9. No claims allowable.

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Sasaki et al. (Blood, Vol. 96, Vol. 11, Part I, page 704a, November 2000) teaches the presence of a poly(A)9 tract in RIX that may be a target of MSI in leukemia. It is noted that leukemia is not a tumor, as required by the instant claims. Leukemia is a blood cancer.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. Goldberg

Jeanine Goldberg
Patent Examiner
March 18, 2004